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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02027528.5

PRIORITY DOCUMENT
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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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Anmeldung Nr:
Application no.: 02027528.5
Demande no:

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Anmelder/Applicant(s)/Demandeur(s):

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ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Tetrahydro-naphthalene derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
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TETRAHYDRO-NAPHTHALENE DERIVATIVES

DETAILED DESCRIPTION OF INVENTION

TECHNICAL FIELD

The present invention relates to a tetrahydro-naphthalenyl derivative which is useful as an active ingredient of pharmaceutical preparations. The tetrahydro-naphthalenyl derivative of the present invention has vanilloid receptor (VR) antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of overactive bladder, urinary incontinence such as urge urinary incontinence, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, and inflammatory disorders such as asthma and chronic obstructive pulmonary (or airways) disease (COPD).

BACKGROUND ART

Vanilloid compounds are characterized by the presence of vanillyl group or a functionally equivalent group. Examples of several vanilloid compounds or vanilloid receptor modulators are vanillin (4-hydroxy-3-methoxy-benzaldehyde), guaiacol (2-methoxy-phenol), zingerone (4-/4-hydroxy-3-methoxyphenyl/-2-butanon), eugenol(2-methoxy4-/2-propenyl/phenol), and capsaicin (8-methy-N-vanillyl-6-noneneamide).

Among others, capsaicin, the main pungent ingredient in "hot" chili peppers, is a specific neurotoxin that desensitizes C-fiber afferent neurons. Capsaicin interacts with vanilloid receptors (VR), which are predominantly expressed in cell bodies of dorsal root ganglia (DRG) or nerve endings of afferent sensory fibers including C-fiber nerve endings [Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert

H, Skinner K, Raumann BE, Basbaum AI, Julius D: The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron. 21: 531-543, 1998]. The VR1 receptor was recently cloned [Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D: Nature 389: 816-824, (1997)] and identified as a nonselective cation channel with six transmembrane domains that is structurally related to the TRP (transient receptor potential) channel family. Binding of capsaicin to VR1 allows sodium, calcium and possibly potassium ions to flow down their concentration gradients, causing initial depolarization and release of neuro-transmitters from the nerve terminals. VR1 can therefore be viewed as a molecular integrator of chemical and physical stimuli that elicit neuronal signals in a pathological conditions or diseases.

There are abundant of direct or indirect evidence that shows the relation between VR1 activity and diseases such as pain, ischaemia, and inflammatory (e.g., WO 99/00115 and 00/50387). Further, it has been demonstrated that VR1 transduce reflex signals that are involved in the overactive bladder of patients who have damaged or abnormal spinal reflex pathways [De Groat WC: A neurologic basis for the overactive bladder. Urology 50 (6A Suppl): 36-52, 1997]. Desensitisation of the afferent nerves by depleting neurotransmitters using VR1 agonists such as capsaicin has been shown to give promising results in the treatment of bladder dysfunction associated with spinal cord injury and multiple sclerosis [(Maggi CA: Therapeutic potential of capsaicin-like molecules - Studies in animals and humans. Life Sciences 51: 1777-1781, 1992) and (DeRidder D; Chandiramani V; Dasgupta P; VanPoppel H; Baert L; Fowler CJ: Intravesical capsaicin as a treatment for refractory detrusor hyperreflexia: A dual center study with long-term followup. J. Urol. 158: 2087-2092, 1997)].

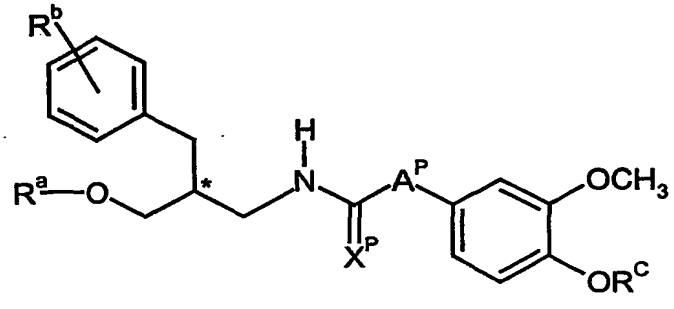
It is anticipated that antagonism of the VR1 receptor would lead to the blockage of neurotransmitter release, resulting in prophylaxis and treatment of the condition and diseases associated with VR1 activity.

It is therefore expected that antagonists of the VR1 receptor can be used for prophylaxis and treatment of the condition and diseases including chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, inflammatory disorders, urinary incontinence (UI) such as urge urinary incontinence (UUI), and/or overactive bladder.

UI is the involuntary loss of urine. UUI is one of the most common types of UI together with stress urinary incontinence (SUI) which is usually caused by a defect in the urethral closure mechanism. UUI is often associated with neurological disorders or diseases causing neuronal damages such as dementia, Parkinson's disease, multiple sclerosis, stroke and diabetes, although it also occurs in individuals with no such disorders. One of the usual causes of UUI is overactive bladder (OAB) which is a medical condition referring to the symptoms of frequency and urgency derived from abnormal contractions and instability of the detrusor muscle.

There are several medications for urinary incontinence on the market today mainly to help treating UUI. Therapy for OAB is focused on drugs that affect peripheral neural control mechanisms or those that act directly on bladder detrusor smooth muscle contraction, with a major emphasis on development of anticholinergic agents. These agents can inhibit the parasympathetic nerves which control bladder voiding or can exert a direct spasmolytic effect on the detrusor muscle of the bladder. This results in a decrease in intravesicular pressure, an increase in capacity and a reduction in the frequency of bladder contraction. Orally active anticholinergic drugs such as propantheline (ProBanthine), tolterodine tartrate (Detrol) and oxybutynin (Ditropan) are the most commonly prescribed drugs. However, their most serious drawbacks are unacceptable side effects such as dry mouth, abnormal visions, constipation, and central nervous system disturbances. These side effects lead to poor compliance. Dry mouth symptoms alone are responsible for a 70% non-compliance rate with oxybutynin. The inadequacies of present therapies highlight the need for novel, efficacious, safe, orally available drugs that have fewer side effects.

WO 00/50387 discloses the compounds having a vanilloid agonist activity represented by the general formula:



wherein;

X^P is an oxygen or sulfur atom;

A^P is $-NHCH_2-$ or $-CH_2-$;

R^a is a substituted or unsubstituted C_{1-4} alkyl group, or $R^{a1}CO-$;

wherein

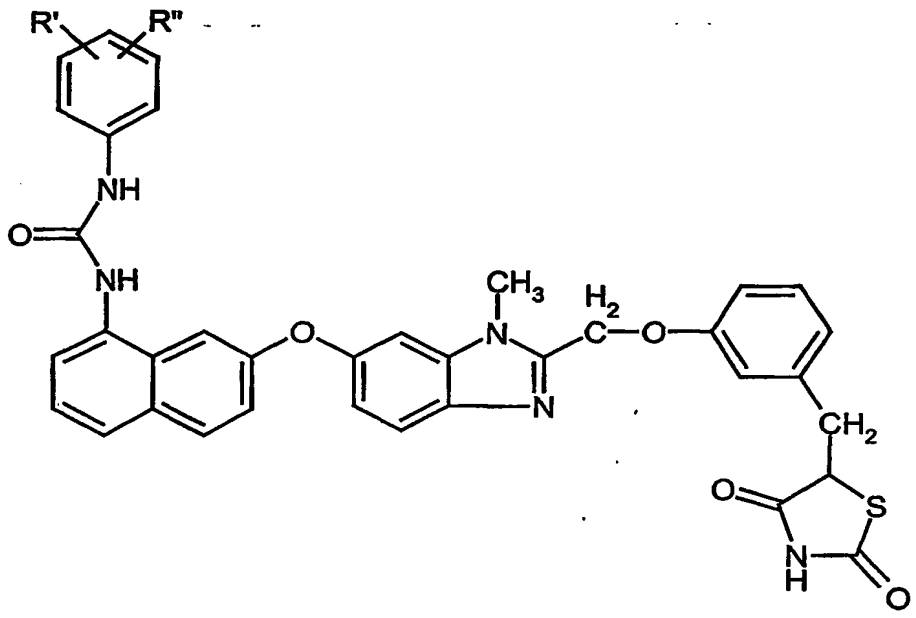
R^{a1} is an alkyl group having 1 to 18 carbon atoms, an alkenyl group having 2 to 18 carbon atoms, or substituted or unsubstituted aryl group having 6 to 10 carbon atoms;

R^b is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, a haloalkyl group having 1 to 6 carbon atoms or a halogen atom;

R^C is a hydrogen atom, an alkyl group having 1 to 4 carbon atom, an aminoalkyl, a diacid monoester or α-alkyl acid; and

the asteric mark * indicates a chiral carbon atom, and their pharmaceutically acceptable salts.

WO 2000/61581 discloses amine derivatives represented by the general formula:

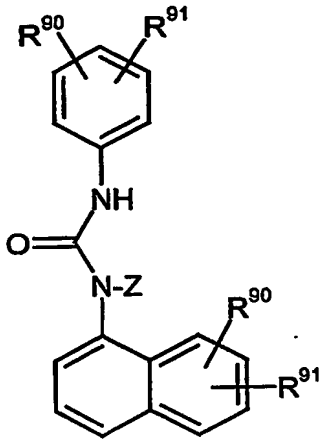


wherein

(R', R") represent (F, F), (CF_3, H), or (iPr, iPr)

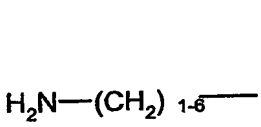
as useful agents for diabetes, hyperlipemia, arteriosclerosis and cancer.

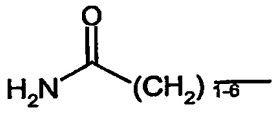
WO 00/75106 discloses the compounds represented by the general formula:

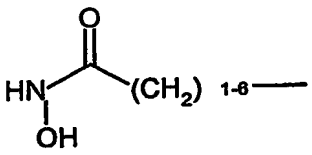


wherein

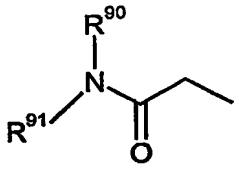
Z represents







or



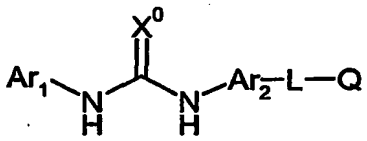
in which

R^{90} is hydrogen, C_{1-12} alkyl, C_{3-8} cycloalkyl, or the like, and R^{91} is amino-C_{1-6} alkyl, aminocarbonyl-C_{1-6} alkyl, or hydroxyaminocarbonyl C_{1-6} alkyl; and

R^{90} and R^{91} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkoxy, fluoro, chloro, bromo, iodo, and nitro;

as useful agents for treating MMP-mediated diseases in mammals.

WO 00/55152 discloses the compounds represented by the general formula:



wherein

Ar_1 is heterocycle;

Ar_2 is tetrahydronapthyl;

X^0 is O or S; and

L and Q are defined in this specification;

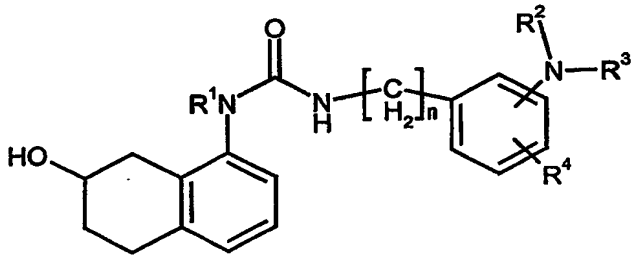
as useful agents for treating inflammation, immune related disease, pain and diabetes.

However, none of these reference discloses simple tetrahydro-naphthalenyl derivatives having VR1 antagonistic activity.

The development of a compound which has effective VR1 antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urinary incontinence, urge urinary incontinence, overactive bladder as well as pain, and/or inflammatory diseases such as asthma and COPD has been desired.

SUMMARY OF THE INVENTION

This invention is to provide a tetrahydro-naphthalenyl derivatives of the formula (I), their tautomeric and stereoisomeric form, and salts thereof:



(I)

wherein

n represents an integer of 0 to 6;

R^1 represents hydrogen or C_{1-6} alkyl;

R^2 and R^3 are identical or different and represent hydrogen, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, or mono-, di-, or tri- halogen,

or

R^2 and R^3 together with the nitrogen atom to which they are attached, form a 3-8 membered saturated heterocyclic ring optionally interrupted by one or two atoms selected from the group consisting of oxygen, sulfur and nitrogen;

wherein

said saturated heterocyclic ring is optionally having substituents selected from the group consisting of halogen, hydroxy, amino, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, and benzyl; and

R^4 represents hydrogen halogen, C_{1-6} alkyl optionally substituted by mono-, di-, or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri-halogen or C_{1-6} alkylthio.

The tetrahydro-naphthalenyl derivatives of formula (I), their tautomeric and stereo-isomeric form, and salts thereof surprisingly show excellent VR1 antagonistic activity. They are, therefore suitable especially for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urinary incontinence, urge urinary incontinence and/or overactive bladder.

The compounds of the present invention are also effective for treating or preventing a disease selected from the group consisting of chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration and/or stroke, as well as inflammatory diseases such as asthma and COPD since the diseases also relate to VR1 activity.

The compounds of the present invention are also useful for the treatment and prophylaxis of neuropathic pain, which is a form of pain often associated with herpes zoster and post-herpetic neuralgia, painful diabetic neuropathy, neuropathic low back pain, posttraumatic and postoperative neuralgia, neuralgia due to nerve compression and other neuralgias, phantom pain, complex regional pain syndromes, infectious or parainfectious neuropathies like those associated with HIV infection, pain associated with central nervous system disorders like multiple sclerosis or Parkinson disease or spinal cord injury or traumatic brain injury, and post-stroke pain.

Furthermore, the compounds of the present invention are useful for the treatment of musculoskeletal pain, forms of pain often associated with osteoarthritis or rheumatoid arthritis or other forms of arthritis, and back pain.

In addition, the compounds of the present invention are useful for the treatment of pain associated with cancer, including visceral or neuropathic pain associated with cancer or cancer treatment.

The compounds of the present invention are furthermore useful for the treatment of visceral pain, e.g. pain associated with obstruction of hollow viscus like gallstone colik, pain associated with irritable bowel syndrome, pelvic pain, vulvodynia, orchialgia or prostatodynia, pain associated with inflammatory lesions of joints, skin, muscles or nerves, and orofascial pain and headache, e.g. migraine or tension-type headache.

In another embodiment, the tetrahydro-naphthalenyl derivatives of formula (I) are those wherein;

n represents an integer of 0 or 1;

R^1 represents hydrogen;

R^2 and R^3 are identical or different and represent hydrogen, or C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, or mono-, di-, or tri- halogen,

or

R^2 and R^3 together with the nitrogen atom to which they are attached, form a 5-7 membered saturated heterocyclic ring optionally interrupted by one or two atoms selected from the group consisting of oxygen, and nitrogen,
wherein
said saturated heterocyclic ring is optionally having substituents selected from the group consisting of oxo, C_{1-6} alkyl, and benzyl; and

R^4 represents hydrogen halogen, C_{1-6} alkyl optionally substituted by mono-, di-, or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri-halogen or C_{1-6} alkylthio.

Yet another embodiment of formula (I) can be those wherein:

n represents an integer of 0 or 1;

R^1 represents hydrogen;

R^2 represents hydrogen or C_{1-6} alkyl;

R^3 represents hydrogen, or C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkyl-amino, or di(C_{1-6} alkyl)amino,

or

R^2 and R^3 together with the nitrogen atom to which they are attached, form a pyrrolidinyl optionally substituted by oxo, piperidino, piperazinyl optionally substituted by benzyl, homopiperidino, or morpholinyl; and

R^4 represents hydrogen, fluoro, chloro, bromo, C_{1-6} alkyl optionally substituted by mono-, di-, or tri- halogen, C_{1-6} alkoxy or C_{1-6} alkylthio.

More preferably, said tetrahydro-naphthalenyl derivative of the formula (I) is selected from the group consisting of:

N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[3-(1-piperidinyl)-4-(trifluoro-methyl)benzyl]urea;

N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[3-(1-pyrrolidinyl)-4-(trifluoro-methyl)benzyl]urea;

N-[4-(1-azepanyl)-3-(trifluoromethyl)benzyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-[3-(1-azepanyl)-4-(trifluoromethyl)benzyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-[3-bromo-4-(1-piperidinyl)benzyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-{[4'-(methylsulfanyl)-6-(1-piperidinyl)-1,1'-biphenyl-3-yl]methyl}urea; and
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[3-(1-pyrrolidinyl)-4-(trifluoromethyl)benzyl]urea.

Further, the present invention provides a medicament, which includes one of the compounds, described above and optionally pharmaceutically acceptable excipients.

Alkyl per se and "alk" and "alkyl" in alkenyl, alkynyl, alkoxy, alkanoyl, alkylamino, alkylaminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl, alkoxycarbonylamino and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino illustratively and preferably represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

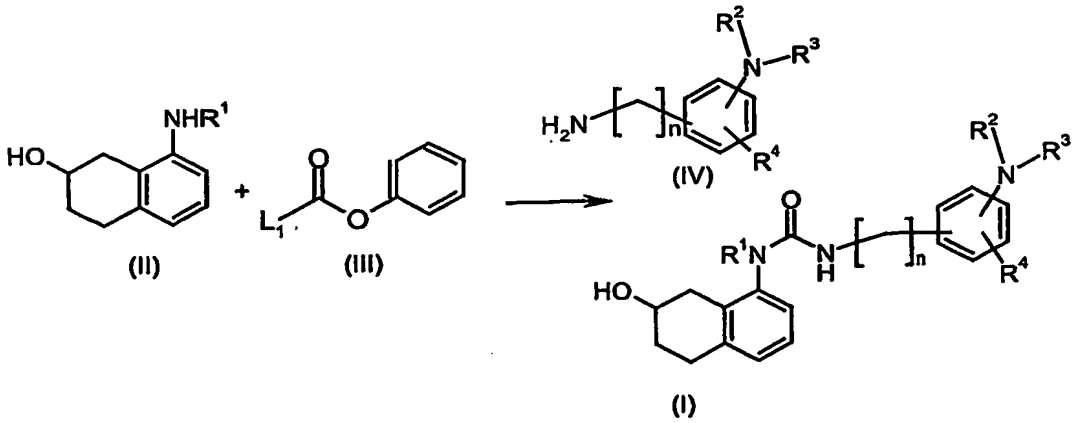
Heterocycle and/or heterocyclic as used herein, designate a closed ring structure, in which one or more of the atoms in the ring is a heteroatom such as sulfur, nitrogen, oxygen, and the like. Suitable examples include, without limitation, pyrrolidinyl, piperidino, piperazinyl, homopiperidino, morpholinyl, thiomorpholinyl, tetrahydrofuryl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and the like.

EMBODIMENT OF THE INVENTION

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by combining various known methods. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts, John Wiley and Sons, New York 1999.

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by the Method [A], [B], [C], [D], [E], [F], [G] or [H] below.

[Method A]



The compound of the formula (I) (wherein n, R^1, R^2, R^3, and R^4 are the same as defined above) can be prepared by reacting the compound of the formula (II) (wherein R^1 is the same as defined above) and the compound of the formula (III) (wherein L_1 represents halogen atom such as chlorine, bromine, or iodine atom) and then adding the compound of the formula (IV) (wherein n, R^2, R^3, and R^4 are the same as defined above) to the reaction mixture.

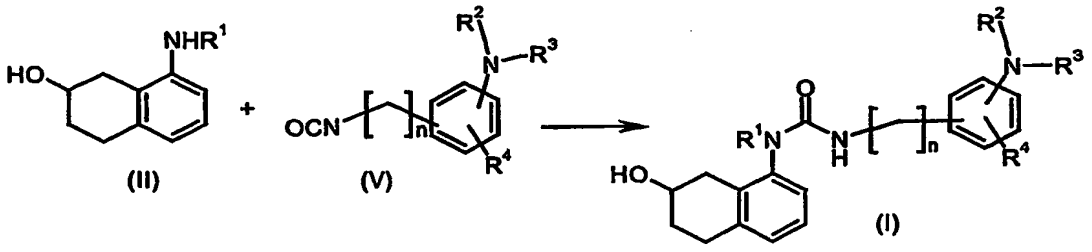
The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50 °C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The reaction can be advantageously carried out in the presence of a base including, for instance, organic amines such as pyridine, triethylamine and N,N-diiso-propylethylamine, dimethylaniline, diethylaniline, 4-dimethylaminopyridine, and others.

The compound (III) and (IV) are commercially available or can be prepared by the use of known techniques.

[Method B]



The compound of the formula (I) (wherein n, R^1, R^2, R^3, and R^4 are the same as defined above) can be prepared by the reaction of the compound of the formula (II) (wherein R^1 is the same as defined above) and the compound of the formula (V) (wherein n, R^2, R^3 and R^4 are the same as defined above).

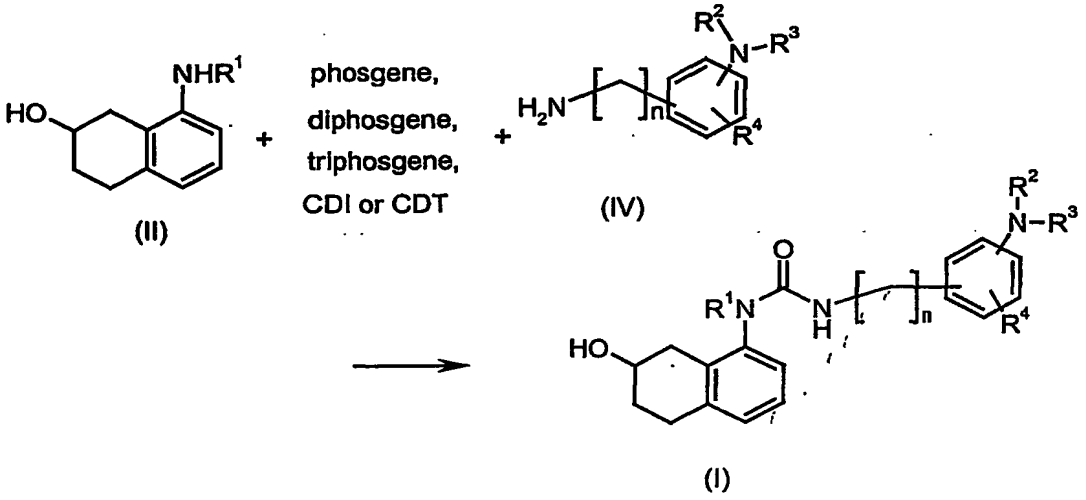
The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction can be carried out in the presence of organic base such as pyridine or triethylamine.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about room temperature to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The compound (V) can be prepared by the use of known techniques or are commercially available.

[Method C]



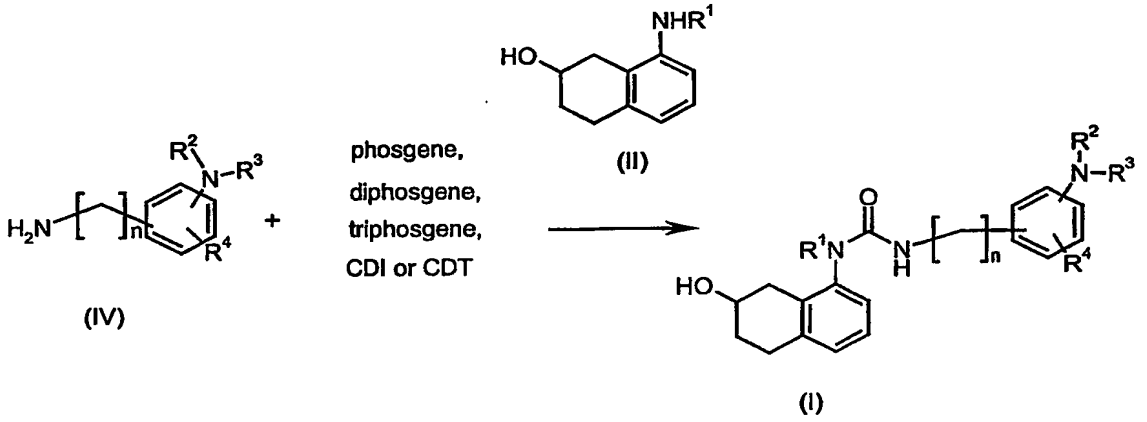
The compound of the formula (I) (wherein n, R^1, R^2, R^3, and R^4 are the same as defined above) can be prepared by reacting the compound of the formula (II) (wherein R^1 is the same as defined above) with phosgene, diphosgene, triphosgene, 1,1-carbonyldiimidazole (CDI), or 1,1'-carbonyldi(1,2,4-triazole)(CDT), and then adding the compound of the formula (IV) (wherein n, R^2, R^3, and R^4 are the same as defined above) to the reaction mixture.

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50°C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

Phosgene, diphosgene, triphosgene, CDI, and CDT are commercially available.

[Method D]



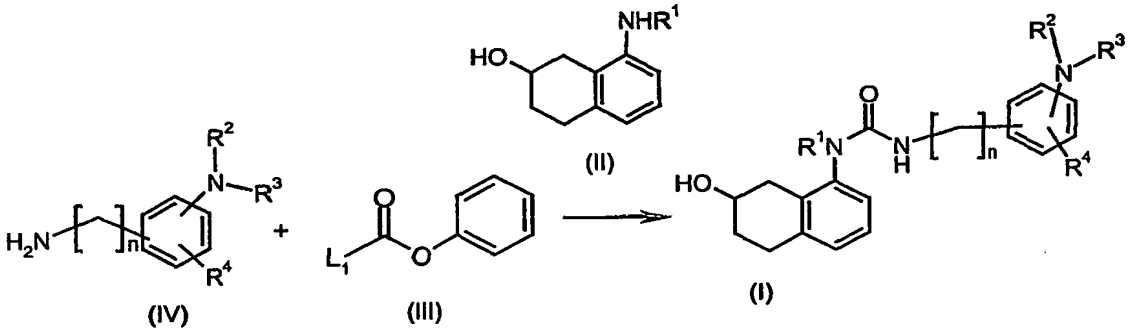
The compound of the formula (I) (wherein n, R^1, R^2, R^3 and R^4 are the same as defined above) can be prepared by reacting the compound of the formula (IV) (wherein n, R^2, R^3, and R^4 are the same as defined above) with phosgene, diphosgene, triphosgene, 1,1-carbonyldiimidazole (CDI), or 1,1'-carbonyldi(1,2,4-triazole)(CDT) and then adding the compound of the formula (II) (wherein R^1 is the same as defined above) to the reaction mixture.

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-

dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50°C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

[Method E]



The compound of the formula (I) (wherein n, R^1, R^2, R^3 and R^4 are the same as defined above) can be prepared by reacting the compound of the formula (IV) (wherein n, R^2, R^3, and R^4 are the same as defined above) and the compound of the formula (III) (wherein L_1 is the same as defined above), and then adding the compound of the formula (II) (wherein R^1 is the same as defined above) to the reaction mixture.

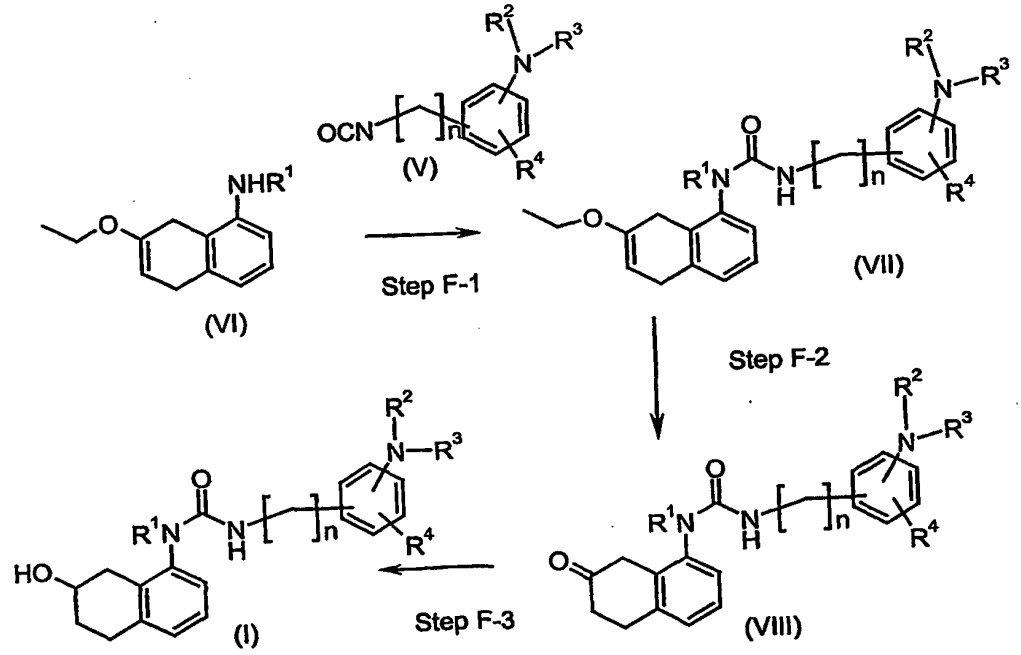
The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-

dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50 °C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The reaction can be advantageously carried out in the presence of a base including, for instance, organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, dimethylaniline, diethylaniline, 4-dimethylaminopyridine, and others.

[Method F]



The compound of the formula (I) (wherein n, R^1, R^2, R^3 and R^4 are the same as defined above) can be prepared by the following procedures in three steps;

In the Step F-1, the compound of the formula (VII) (wherein n, R^1, R^2, R^3 and R^4 are the same as defined above) can be prepared by reacting the compound of the formula (VI) (wherein R^1 is the same as defined above) with the compound of the formula (V) (wherein n, R^2, R^3 and R^4 are the same as defined above) in the same manner described in Method B for the preparation of the compound of the formula (I).

In the Step F-2, the compound of the formula (VIII) (wherein n, R^1, R^2, R^3, and R^4 are the same as defined above) can be prepared by reacting the compound of the formula (VII) (wherein n, R^1, R^2, R^3, and R^4 are the same as defined above) with an acid such as hydrochloric acid.

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; alcohols such as methanol, ethanol; water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

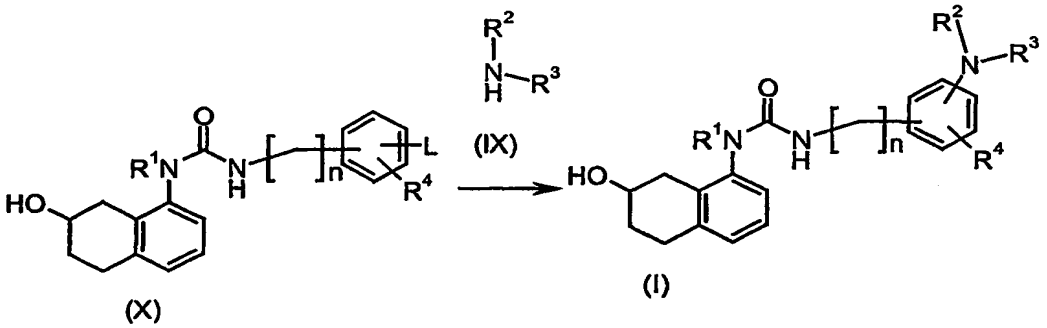
In the Step F-3, the compound of the formula (I) (wherein n, R^1, R^2, R^3 and R^4 are the same as defined above) can be prepared by reacting the compound of the formula (VIII) (wherein n, R^1, R^2, R^3 and R^4 are the same as defined above) with reducing agent such as sodium borohydride or lithium aluminum hydride.

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; alcohols such as methanol, ethanol, isopropanol, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50°C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The compound (VI) is commercially available or can be prepared by the use of known techniques.

[Method G]



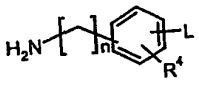
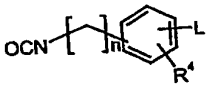
The compound of the formula (I) (wherein n, R^1, R^2, R^3 and R^4 are the same as defined above) can be obtained by the reaction of the compound of the formula (X) (wherein n, R^1, R^2, R^3, R^4 and L are the same as defined above) with the compound of the formula (IX) (wherein R^2 and R^3 are the same as defined above).

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides

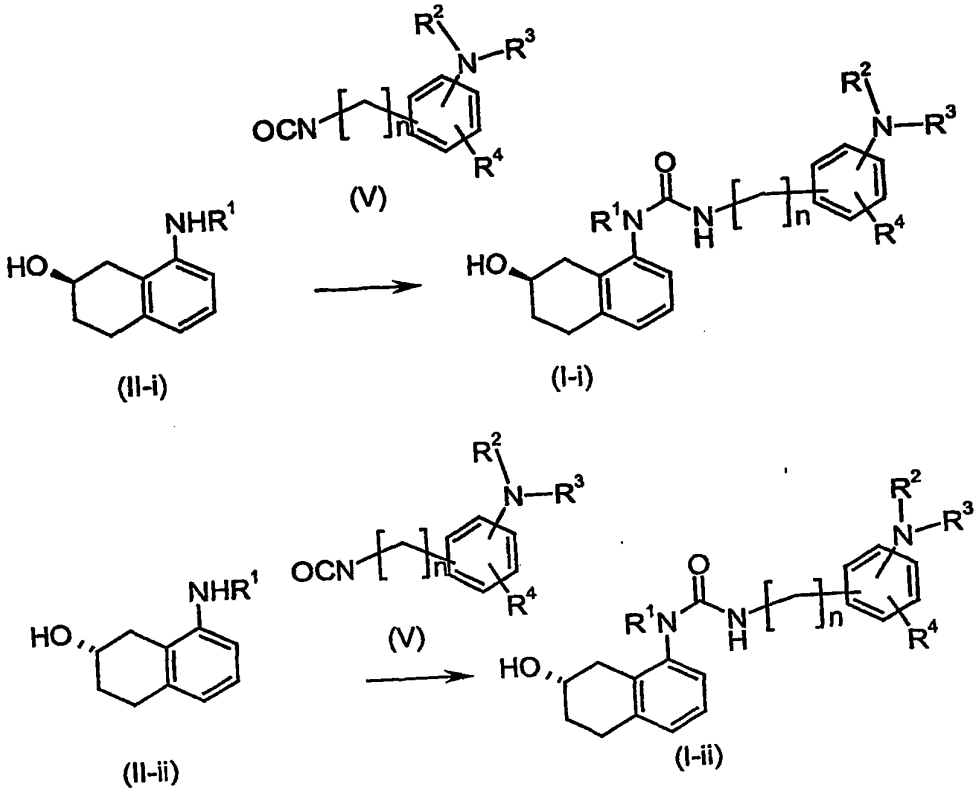
such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction can be advantageously carried out in the presence of an catalyst such as palladium catalysts and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 60 hours and preferably 1 to 48 hours.

The compound (X) can be prepared in the similar manner as described in Method [A], [B], [C], [D], [E], or [F] for the preparation of the compound of the formula (I) using a compound (IV')  or (V')  (wherein n, L and R^4 are the same as defined above) instead of the compound (IV) or (V).

[Method H]



The stereoisomeric form of the compound (I), R form (I-i) (wherein n, R^1, R^2, R^3, and R^4 are the same as defined above) can be prepared by the reaction of the compound of the formula (II-i) (wherein R^1 is the same as defined above) with the compound of the formula (V) (wherein n, R^2, R^3, and R^4 are the same as defined above) in the same manner described in Method B for the preparation of the compound of the formula (I).

The stereoisomeric form of the compound (I), S form (I-ii) (wherein n, R^1, R^2, R^3, and R^4 are the same as defined above) can be prepared by the reaction of the compound of (II-ii) (wherein R^1 is the same as defined above) with the compound of the formula (V) (wherein n, R^1, R^2, R^3, and R^4 are the same as defined above) in the same manner described in Method B for the preparation of the compound of the formula (I).

The compound (II-i) or (II-ii) can be prepared by the use of known techniques.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salt thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients therefore. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in

the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxy-methyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable

carriers, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg /kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100mg /kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

EXAMPLES

The present invention will be described as a form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

Mass spectra were obtained using electrospray (ES) ionization techniques (micromass Platform LC). Melting points are uncorrected. Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column(4.6 mmϕ X 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow rate. TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Great Britain, Tokyo kasei kogyo Co., Ltd., Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Merck KgaA, Germany, Kanto Chemical Co., Ltd.

^{1}H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ^{1}H) spectrometer or Brucker 500 UltraShieled™ (500 MHz for 1H) . Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, m, and br refer to singlet, doblet, triplet, quartet, multiplet, and broad, respectively. The mass determinations were carried out by MAT95 (Finnigan MAT).

All starting materials are commercially available or can be prepared using methods cited in the literature.

The effect of the present compounds was examined by the following assays and pharmacological tests.

[Measurement of capsaicin-induced Ca^{2+} influx in the human VR1-transfected CHO cell line] (Assay 1)

(1) Establishment of the human VR1-CHOluc9aeq cell line

Human vanilloid receptor (hVR1) cDNA was cloned from libraries of axotomized dorsal root ganglia (WO 00/29577). The cloned hVR1 cDNA was constructed with pcDNA3 vector and transfected into a CHOluc9aeq cell line. The cell line contains aequorin and CRE-luciferase reporter genes as read-out signals. The transfectants were cloned by limiting dilution in selection medium (DMEM/F12 medium (Gibco BRL) supplemented with 10% FCS, 1.4 mM Sodium pyruvate, 20 mM HEPES, 0.15% Sodium bicarbonate, 100 U/ml penicillin, 100 μg/ml streptomycin, 2 mM glutamine, non-essential amino acids and 2 mg/ml G418). Ca^{2+} influx was examined in the capsaicin-stimulated clones. A high responder clone was selected and used for further experiments in the project. The human VR1-CHOluc9aeq cells were maintained in the selection medium and passaged every 3-4 days at 1-2.5x10^5 cells/flask (75 mm^2).

(2) Measurement of Ca^{2+} influx using FDSS-3000

Human VR1-CHOluc9aeq cells were suspended in a culture medium which is the same as the selection medium except for G418 and seeded at a density of 1,000 cells per well into 384-well plates (black walled clear-base / Nalge Nunc International). Following the culture for 48 hrs the medium was changed to 2 μM Fluo-3 AM (Molecular Probes) and 0.02% Puronic F-127 in assay buffer (Hank's balanced salt solution (HBSS), 17 mM HEPES (pH7.4), 1 mM Probenecid, 0.1% BSA) and the cells were incubated for 60 min at

25°C. After washing twice with assay buffer the cells were incubated with a test compound or vehicle for 20 min at 25°C. Mobilization of cytoplasmic Ca^{2+} was measured by FDSS-3000 (λ_{ex}=488nm, λ_{em}=540nm / Hamamatsu Photonics) for 60 sec after the stimulation with 10 nM capsaicin. Integral R was calculated and compared with controls.

[Measurement of the capsaicin-induced Ca^{2+} influx in primary cultured rat dorsal root ganglia neurons] (Assay 2)

(1) Preparation of rat dorsal root ganglia neurons

New born Wister rats (5-11 days) were sacrificed and dorsal root ganglia (DRG) was removed. DRG was incubated with 0.1% trypsin (Gibco BRL) in PBS(-) (Gibco BRL) for 30 min at 37°C, then a half volume of fetal calf serum (FCS) was added and the cells were spun down. The DRG neuron cells were resuspended in Ham F12/5% FCS/5% horse serum (Gibco BRL) and dispersed by repeated pipetting and passing through 70 μm mesh (Falcon). The culture plate was incubated for 3 hours at 37°C to remove contaminating Schwann cells. Non-adherent cells were recovered and further cultured in laminin-coated 384 well plates (Nunc) at $1x10^4$ cells/50 μl/well for 2 days in the presence of 50 ng/ml recombinant rat NGF (Sigma) and 50 μM 5-fluorodeoxyuridine (Sigma).

(2) Ca^{2+} mobilization assay

DRG neuron cells were washed twice with HBSS supplemented with 17 mM HEPES (pH 7.4) and 0.1% BSA. After incubating with 2 μM fluo-3AM (Molecular Probe), 0.02% PF127 (Gibco BRL) and 1 mM probenecid (Sigma) for 40 min at 37°C, cells were washed 3 times. The cells were incubated with VR1 antagonists or vehicle (dimethylsulphoxide) and then with 1 μM capsaicin in FDSS-6000 (λ_{ex}=480nm, λ_{em}=520nm / Hamamatsu

Photonics). The fluorescence changes at 480nm were monitored for 2.5 min. Integral R was calculated and compared with controls.

[Organ bath assay to measure the capsaicin-induced bladder contraction] (Assay 3)

Male Wistar rats (10 week old) were anesthetized with ether and sacrificed by dislocating the necks. The whole urinary bladder was excised and placed in oxygenated Modified Krebs-Henseleit solution (pH 7.4) of the following composition (112mM NaCl, 5.9mM KCl, 1.2mM $MgCl_2$, 1.2mM NaH_2PO_4, 2mM $CaCl_2$, 2.5mM $NaHCO_3$, 12mM glucose). Contractile responses of the urinary bladder were studied as described previously [Maggi CA et al: Br.J.Pharmacol. 108: 801-805, 1993]. Isometric tension was recorded under a load of 1 g using longitudinal strips of rat detrusor muscle. Bladder strips were equilibrated for 60 min before each stimulation. Contractile response to 80 mM KCl was determined at 15 min intervals until reproducible responses were obtained. The response to KCl was used as an internal standard to evaluate the maximal response to capsaicin. The effects of the compounds were investigated by incubating the strips with compounds for 30 min prior to the stimulation with 1 μM capsaicin (vehicle: 80% saline, 10% EtOH, and 10% Tween 80). One of the preparations made from the same animal was served as a control while the others were used for evaluating compounds. Ratio of each capsaicin-induced contraction to the internal standard (i.e. KCl-induced contraction) was calculated and the effects of the test compounds on the capsaicin-induced contraction were evaluated.

[Measurement of Ca^{2+} influx in the human P2X1-transfected CHO cell line]

(1) Preparation of the human P2X1-transfected CHOluc9aeq cell line

Human P2X1-transfected CHOluc9aeq cell line was established and maintained in Dulbecco's modified Eagle's medium (DMEM/F12)

supplemented with 7.5% FCS, 20 mM HEPES-KOH (pH 7.4), 1.4 mM sodium pyruvate, 100 U/ml penicillin, 100 μg/ml streptomycin, 2 mM glutamine (Gibco BRL) and 0.5 Units/ml apyrase (grade I, Sigma). The suspended cells were seeded in each well of 384-well optical bottom black plates (Nalge Nunc International) at 3 x 10^3 / 50 μl / well. The cells were cultured for following 48 hrs to adhere to the plates.

(2) Measurement of the intracellular Ca^{2+} levels

P2X1 receptor agonist-mediated increases in cytosolic Ca^{2+} levels were measured using a fluorescent Ca^{2+} chelating dye, Fluo-3 AM (Molecular Probes). The plate-attached cells were washed twice with washing buffer (HBSS, 17 mM HEPES-KOH (pH 7.4), 0.1% BSA and 0.5 units/ml apyrase), and incubated in 40 μl of loading buffer (1 μM Fluo-3 AM, 1 mM probenecid, 1 μM cyclosporin A, 0.01% pluronic (Molecular Probes)in washing buffer) for 1 hour in a dark place. The plates were washed twice with 40 μl washing buffer and 35 μl of washing buffer were added in each well with 5 μl of test compounds or *2',3'-o*-(2,4,6-trinitrophenyl) adenosine 5'-triphpsphate (Molecular Probes) as a reference. After further incubation for 10 minutes in dark 200 nM α, β-methylene ATP agonist was added to initiate the Ca^{2+} mobilization. Fluorescence intensity was measured by FDSS-6000 (λ_{ex}=410nm, λ_{em}=510nm / Hamamatsu Photonics) at 250 msec intervals. Integral ratios were calculated from the data and compared with that of a control.

[Measurement of capsaicin-induced bladder contraction in anesthetized rats] (Assay 4)

(1) Animals

Female Sprague-Dawley rats (200~250 g / Charles River Japan) were used.

(2) Catheter implantation

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.2 g/kg. The abdomen was opened through a midline incision, and a polyethylene catheter (BECTON DICKINSON, PE50) was implanted into the bladder through the dome. In parallel, the inguinal region was incised, and a polyethylene catheter (Hibiki, size 5) filled with 2 IU / ml of heparin (Novo Heparin, Aventis Pharma) in saline (Otsuka) was inserted into a common iliac artery.

(3) Cystometric investigation

The bladder catheter was connected via T-tube to a pressure transducer (Viggo-Spectramed Pte Ltd, DT-XXAD) and a microinjection pump (TERUMO). Saline was infused at room temperature into the bladder at a rate of 2.4 ml/hr. Intravesical pressure was recorded continuously on a chart pen recorder (Yokogawa). At least three reproducible micturition cycles, corresponding to a 20-minute period, were recorded before a test compound administration and used as baseline values.

(4) Administration of test compounds and stimulation of bladder with capsaicin

The saline infusion was stopped before administrating compounds. A testing compound dissolved in the mixture of ethanol, Tween 80 (ICN Biomedicals

Inc.) and saline (1 : 1 : 8, v/v/v) was administered intraarterially at 10 mg/kg. 2min after the administration of the compound 10 μg of capsaicin (Nacalai Tesque) dissolved in ethanol was administered intraarterially.

(5) Analysis of cystometry parameters

Relative increases in the capsaicin-induced intravesical pressure were analyzed from the cystometry data. The capsaicin-induced bladder pressures were compared with the maximum bladder pressure during micturition without the capsaicin stimulation. The testing compounds–mediated inhibition of the increased bladder pressures was evaluated using Student's t-test. A probability level less than 5% was accepted as significant difference.

[Measurement of over active bladder in anesthetized cystitis rats] (Assay 5)

(1) Animals

Female Sprague-Dawley rats (180~250 g / Charles River Japan) were used. Cyclophosphamide (CYP) dissolved in saline was administered intra-peritoneally at 150 mg/kg 48 hours before experiment.

(2) Catheter implantation

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.25 g/kg. The abdomen was opened through a midline incision, and a polyethylene catheter (BECTON DICKINSON, PE50) was implanted into the bladder through the dome. In parallel, the inguinal region was incised, and a polyethylene catheter (BECTON DICKINSON, PE50) filled with saline (Otsuka) was inserted into a femoral vein. After the bladder was emptied, the rats were left for 1 hour for recovery from the operation.

(3) Cystometric investigation

The bladder catheter was connected via T-tube to a pressure transducer (Viggo-Spectramed Pte Ltd, DT-XXAD) and a microinjection pump (TERUMO). Saline was infused at room temperature into the bladder at a rate of 3.6 ml/hr for 20 min. Intravesical pressure was recorded continuously on a chart pen recorder (Yokogawa). At least three reproducible micturition cycles, corresponding to a 20-minute period, were recorded before a test compound administration.

(4) Administration of test compounds

A testing compound dissolved in the mixture of ethanol, Tween 80 (ICN Biomedicals Inc.) and saline (1 : 1 : 8, v/v/v) was administered intravenously at 0.05 mg/kg, 0.5 mg/kg or 5 mg/kg. 3min after the administration of the compound, saline (Nacalai Tesque) was infused at room temperature into the bladder at a rate of 3.6 ml/hr.

(5) Analysis of cystometry parameters

The cystometry parameters were analyzed as described previously [Lecci A et al: Eur. J. Pharmacol. 259: 129-135, 1994]. The micturition frequency calculated from micturition interval and the bladder capacity calculated from a volume of infused saline until the first micturition were analyzed from the cystometry data. The testing compounds–mediated inhibition of the frequency and the testing compounds–mediated increase of bladder capacity were evaluated using unpaired Student's t-test. A probability levels less than 5% was accepted as significant difference. Data were analyzed as the mean $\pm$ SEM from 4 – 7 rats.

[Measurement of Acute Pain]

Acute pain is measured on a hot plate mainly in rats. Two variants of hot plate testing are used: In the classical variant animals are put on a hot surface (52 to 56 °C) and the latency time is measured until the animals show nociceptive behavior, such as stepping or foot licking. The other variant is an increasing temperature hot plate where the experimental animals are put on a surface of neutral temperature. Subsequently this surface is slowly but constantly heated until the animals begin to lick a hind paw. The temperature which is reached when hind paw licking begins is a measure for pain threshold.

Compounds are tested against a vehicle treated control group. Substance application is performed at different time points via different application routes (i.v., i.p., p.o., i.t., i.c.v., s.c., intradermal, transdermal) prior to pain testing.

[Measurement of Persistent Pain]

Persistent pain is measured with the formalin or capsaicin test, mainly in rats. A solution of 1 to 5% formalin or 10 to 100 µg capsaicin is injected into one hind paw of the experimental animal. After formalin or capsaicin application the animals show nociceptive reactions like flinching, licking and biting of the affected paw. The number of nociceptive reactions within a time frame of up to 90 minutes is a measure for intensity of pain.

Compounds are tested against a vehicle treated control group. Substance application is performed at different time points via different application routes (i.v., i.p., p.o., i.t., i.c.v., s.c., intradermal, transdermal) prior to formalin or capsaicin administration.

[Measurement of Neuropathic Pain]

Neuropathic pain is induced by different variants of unilateral sciatic nerve injury mainly in rats. The operation is performed under anesthesia. The first variant of sciatic nerve injury is produced by placing loosely constrictive ligatures around the common sciatic nerve (Bennett and Xie, Pain 33 (1988): 87-107). The second variant is the tight ligation of about the half of the diameter of the common sciatic nerve (Seltzer et al., Pain 43 (1990): 205-218). In the next variant, a group of models is used in which tight ligations or transections are made of either the L5 and L6 spinal nerves, or the L5 spinal nerve only (KIM SH; CHUNG JM, AN EXPERIMENTAL-MODEL FOR PERIPHERAL NEUROPATHY PRODUCED BY SEGMENTAL SPINAL NERVE LIGATION IN THE RA, PAIN 50 (3) (1992): 355-363). The fourth variant involves an axotomy of two of the three 'terminal branches of the sciatic nerve (tibial and common peroneal nerves) leaving the remaining sural nerve intact whereas the last variant comprises the axotomy of only the tibial branch leaving the sural and common nerves uninjured. Control animals are treated with a sham operation.

Postoperatively, the nerve injured animals develop a chronic mechanical allodynia, cold allodynioa, as well as a thermal hyperalgesia. Mechanical allodynia is measured by means of a pressure transducer (electronic von Frey Anesthesiometer, IITC Inc.-Life Science Instruments, Woodland Hills, SA, USA; Electronic von Frey System, Somedic Sales AB, Hörby, Sweden). Thermal hyperalgesia is measured by means of a radiant heat source (Plantar Test, Ugo Basile, Comerio, Italy), or by means of a cold plate of 5 to 10 °C where the nocifensive reactions of the affected hind paw are counted as a measure of pain intensity. A further test for cold induced pain is the counting of nocifensive reactions, or duration of nocifensive responses after plantar administration of acetone to the affected hind limb. Chronic pain in general is assessed by registering the circadanian rhytms in activity (Surjo and Arndt,

Universität zu Köln, Cologne, Germany), and by scoring differences in gait (foot print patterns; FOOTPRINTS program, Klapdor et al., 1997. A low cost method to analyse footprint patterns. J. Neurosci. Methods 75, 49-54).

Compounds are tested against sham operated and vehicle treated control groups. Substance application is performed at different time points via different application routes (i.v., i.p., p.o., i.t., i.c.v., s.c., intradermal, transdermal) prior to pain testing.

[Measurement of Inflammatory Pain]

Inflammatory pain is induced mainly in rats by injection of 0.75 mg carrageenan or complete Freund's adjuvant into one hind paw. The animals develop an edema with mechanical allodynia as well as thermal hyperalgesia. Mechanical allodynia is measured by means of a pressure transducer (electronic von Frey Anesthesiometer, IITC Inc.-Life Science Instruments, Woodland Hills, SA, USA). Thermal hyperalgesia is measured by means of a radiant heat source (Plantar Test, Ugo Basile, Comerio, Italy, Paw thermal stimulator, G. Ozaki, University of California, USA). For edema measurement two methods are being used. In the first method, the animals are sacrificed and the affected hindpaws sectioned and weighed. The second method comprises differences in paw volume by measuring water displacement in a plethysmometer (Ugo Basile, Comerio, Italy).

Compounds are tested against uninflamed as well as vehicle treated control groups. Substance application is performed at different time points via different application routes (i.v., i.p., p.o., i.t., i.c.v., s.c., intradermal, transdermal) prior to pain testing.

[Measurement of Diabetic Neuropathic Pain]

Rats treated with a single intraperitoneal injection of 50 to 80 mg/kg streptozotocin develop a profound hyperglycemia and mechanical allodynia within 1 to 3 weeks. Mechanical allodynia is measured by means of a pressure transducer (electronic von Frey Anesthesiometer, IITC Inc.-Life Science Instruments, Woodland Hills, SA, USA).

Compounds are tested against diabetic and non-diabetic vehicle treated control groups. Substance application is performed at different time points via different application routes (i.v., i.p., p.o., i.t., i.c.v., s.c., intradermal, transdermal) prior to pain testing.

Results of IC_{50} of capsaicin-induced Ca^{2+} influx in the human VR1-transfected CHO cell line are shown in Examples and tables of the Examples below. The data corresponds to the compounds as yielded by solid phase synthesis and thus to levels of purity of about 40 to 90%. For practical reasons, the compounds are grouped in four classes of activity as follows:

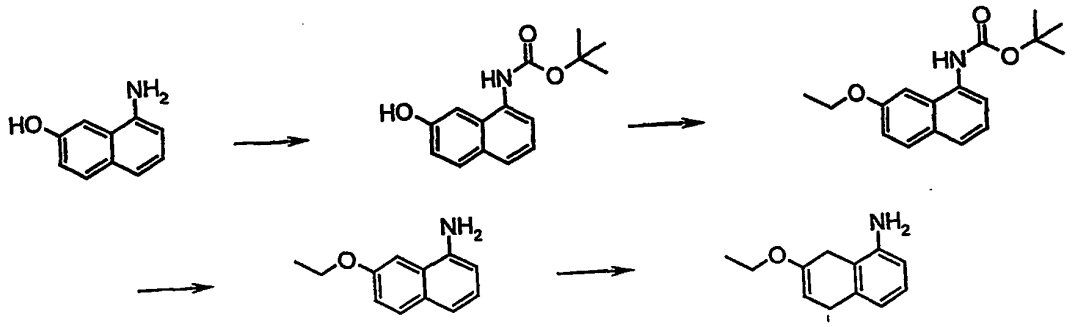
IC_{50} = A (< or =) 0.1 μM < B (< or =) 0.5 μM < C (< or =) 1 μM < D

The compounds of the present invention also show excellent selectivity, and strong activity in other assays (2)-(5) described above.

Preparing method of starting compounds

[Starting compound A]

7-ethoxy-5,8-dihydronaphthalen-1-ylamine



To a stirred solution of 8-amino-2-naphthol (50.0 g, 314 mmol) in tetrahydrofuran (1000 mL) was added di-t-butyldicarbonate (68.6 g, 314 mmol). The mixture was stirred at 70°C for 18 hours. After the mixture was cooled to room temperature, solvent was removed under reduced pressure. To the residue was added ethylacetate, and washed with saturated aqueous solution of sodium carbonate and then with water. The extracted organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the obtained residue was added diisopropyl ether, and the precipitate was filtered and dried to afford N-t-butoxycarbonyl-8-amino-2-naphthol (64.2 g, 79 % yield).

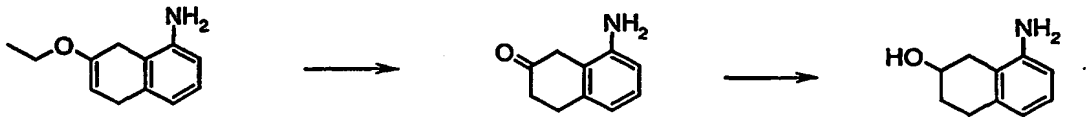
Next, to a mixture of N-t-butoxycarbonyl-8-amino-2-naphthol (64.0 g, 247 mmol) and Cesium carbonate (161 g, 493 mmol) in 300 mL anhydrous DMF was added iodoethane (42.3 g, 272 mmol) at room temperature. The mixture was stirred at 60°C for 2 hours. Water was added to the mixture, and the product was extracted with ethylacetate. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the obtained residue was added diisopropyl ether and the precipitate was collected and dried to afford (7-ethoxy-naphthalen-1-yl)-carbamic acid t-butyl ester (47.9 g, 67.5 % yield).

Next, to a (7-ethoxy-naphthalen-1-yl)-carbamic acid t-butyl ester (47.9 g, 167 mmol) in 100 mL anhydrous 1,4-dioxane was added 4N HCl in 1,4-dioxane (100 mL) at 0°C. The mixture was stirred at room temperature for 2 hours. Diisopropyl ether was added to the reaction mixture and the precipitate was filtered. To the obtained solid was added saturated sodium bicarbonate and the product was extracted with ethylacetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 7-ethoxy-naphthalen-1-ylamine (27.0 g, 86.3 % yield).

Next, to a flask containing a mixture of 7-ethoxy-naphthalen-1-ylamine (1.80 g, 9.61 mmol) and t-buthanol (2.13 g, 28.8 mmol) in tetrahydrofuran (20 mL) was collected liquid ammonia (300 mL) at -78°C. To the mixture was added lithium (0.200 g, 28.8 mmol) over 30 minutes and stirred at -78°C for 1 hour. Methanol and water was added, and the mixture was stirred at room temperature for 16 hours to allow ammonia to evaporate. To the obtained residue was added ethylacetate. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 7-ethoxy-5,8-dihydronaphthalen-1-ylamine (1.37 g, 76 % yield).

[Starting compound B]

8-amino-1,2,3,4-tetrahydro-naphthalen-2-ol



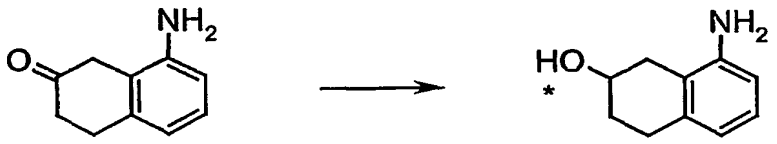
To a stirred solution of 7-ethoxy-5,8-dihydronaphthalen-1-ylamine (1.07 g, 5.65 mmol) in tetrahydrofuran (30 mL) was added solution of aqueous 2N HCl (10 mL), and stiired at 40°C for 1 hour. The mixture was neutralized with addition of sodium bicorbonate, and the product was extracted with ethylacetate. The organic

layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 8-amino-3,4-dihydro-1H-naphthalen-2-one (0.71 g, 78 % yield).

Next, to 8-amino-3,4-dihydro-1H-naphthalen-2-one (0.050 g, 0.318 mmol) in methanol (10 mL) was added sodium borohydride (0.030 g, 0.175 mmol) at 0°C, and the mixture was stirred for 1 hour. The mixture was poured into water, and the product was extracted with ethylacetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 8-amino-1,2,3,4-tetrahydro-naphthalen-2-ol (0.037 g, 71 % yield).

[Starting compound C]

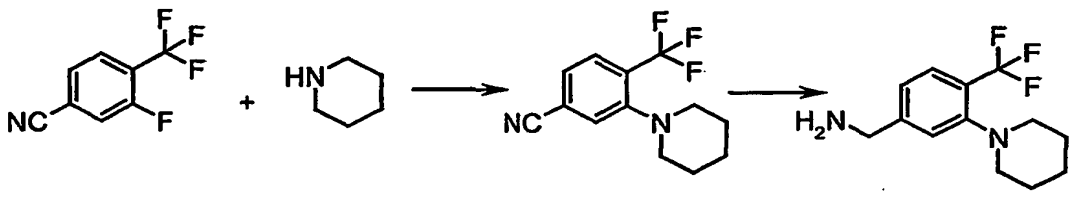
chiral 8-amino-1,2,3,4-tetrahydro-naphthalen-2-ol enantiomer



To a stirred solution of benzeneruthenium(II) chloride dimer (3.10 mg, 0.006 mmol) and (1S, 2R)-(-)-cis-1-amino-2-indanol (3.7 mg, 0.025 mmol) in degaussed isopropanol was heated at 80°C for 20 minutes under argon. The mixture was added to the solution of 8-amino-3,4-dihydro-1H-naphthalen-2-one (50 mg, 0.310 mmol) in isopropanol (3 mL) at room temperature. A solution of potassium hydroxide (3.48 mg, 0.062 mmol) in isopropanol (1 mL) was added, and the mixture was stiired at 45°C for 1 hour. The mixture was passed through silica gel and washed with ethylacetate. The filtrate was concentrated under reduced pressure to afford the chiral 8-amino-1,2,3,4-tetrahydro-naphthalen-2-ol enantiomer (33.0 mg, 65 % yield).

[Starting compound D]

3-piperidin-1-yl-4-trifluoromethyl-benzylamine

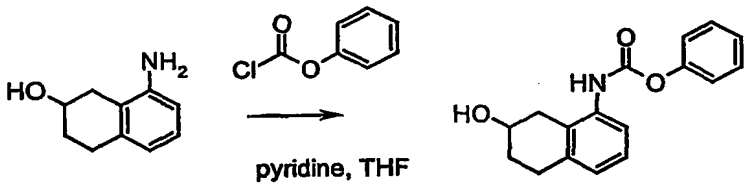


To a solution of 3-fluoro-4-trifluoromethyl-benzonitrile (300 mg, 1.59 mmol) in DMSO (5.0 mL) was added piperidine (675 mg, 7.93 mmol), and the mixture was stirred for 43 hours at 55 °C. After the mixture was cooled to room temperature, ethylacetate was added and washed with water then brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (hexane : ethylacetate = 10 : 1) to afford 3-piperidin-1-yl-4-trifluoromethyl-benzonitrile (353 mg, 88 % yield).

Next, to a suspension of lithium aluminum hydride (44.8 mg, 1.18 mmol) in tetrahydrofuran (5.0 mL) was added 3-piperidin-1-yl-4-trifluoromethyl-benzonitrile (100.0 mg, 0.39 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour and at room temperature for 14 hours. To the mixture was added water and extracted with ethylacetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (methanol : ethylacetate = 1 : 2) to afford 3-piperidin-1-yl-4-trifluoromethyl-benzylamine (46.8 mg, 46 % yield).

[Starting compound E]

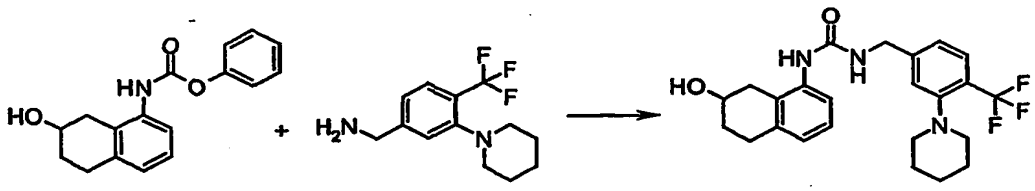
(7-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-carbamic acid phenyl ester



To a stirred solution of 8-amino-1,2,3,4-tetrahydro-naphthalen-2-ol (30.0 mg, 0.18 mmol) and pyridine (21.8 mg, 0.28 mmol) in 1.0 mL THF was added phenyl chloroformate (30.2 mg, 0.19 mmol), and the mixture was stirred for 1 hour at room temperature. To the product mixture was added water and extracted with ethylacetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was triturated with ethylacetate and hexane to afford (7-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-carbamic acid phenyl ester (25.2 mg, 48 % yield).

Example 1-1

N-(7-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-N'-(3-piperidin-1-yl-4-trifluoromethyl-benzyl)-urea



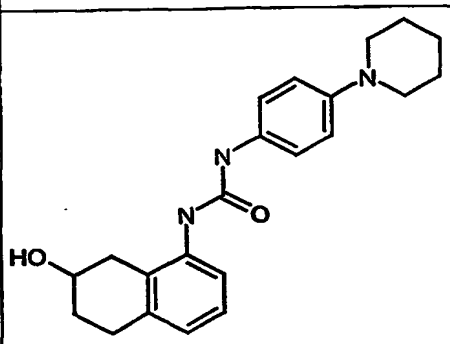
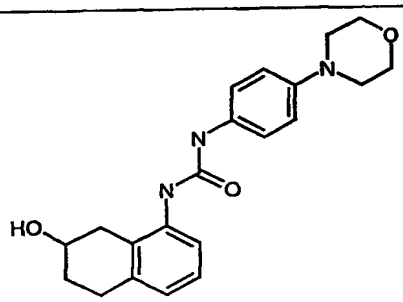
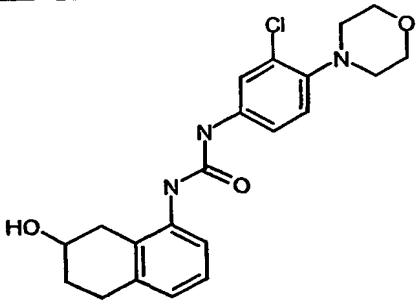
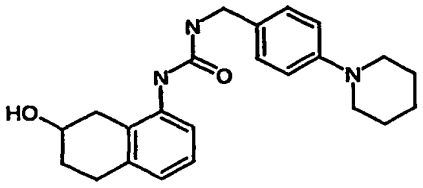
To (7-Hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-carbamic acid phenyl ester (41.1 mg, 0.15 mmol) in DMSO (1.0 mL) was added 3-piperidin-1-yl-4-trifluoromethyl-benzylamine (45.0 mg, 0.17 mmol) at room temperature. The mixture was stirred for 1 hour and extracted with ethylacetate. The organic layer was washed with water

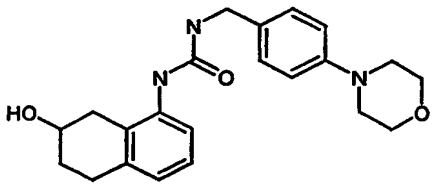
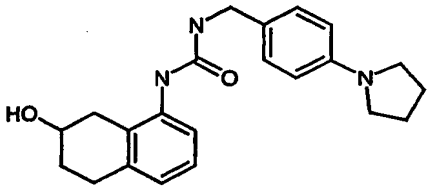
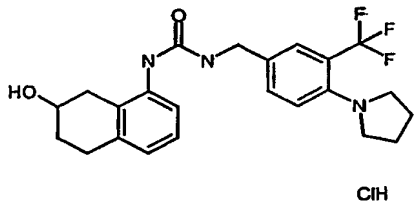
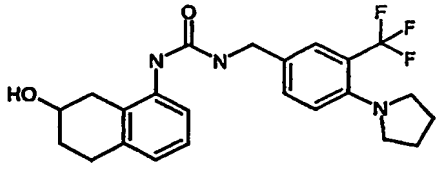
then brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solid was washed with diethylether to obtain N-(7-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl)-N'-(3-piperidin-1-yl-4-trifluoromethyl-benzyl)-urea (44.6 mg, 69 % yield).

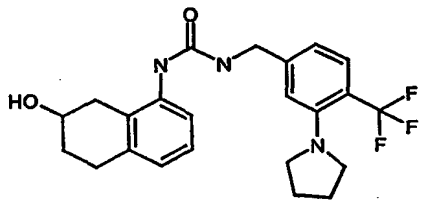
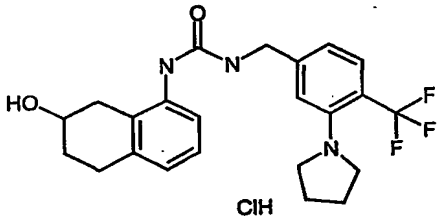
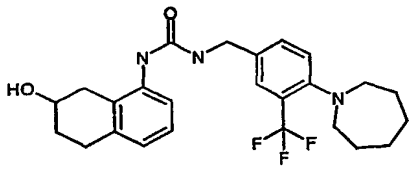
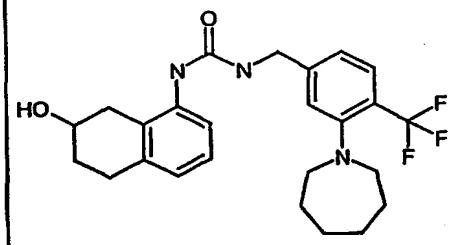
^{1}H NMR (300M Hz, aceton): δ 1.56 - 1.70 (7H, m), 1.96 (1H, m), 2.49 (1H, dd), 2.75 (1H, m), 2.84 - 2.96 (6H, m), 4.05 (1H, m), 4.46 (2H, d), 6.67 (1H, brt), 6.79 (1H, d), 7.03 (1H, t), 7.26 (1H, d), 7.33 (1H, s), 7.48 (1H, s), 7.59 (1H, d), 7.67 (1H, d).

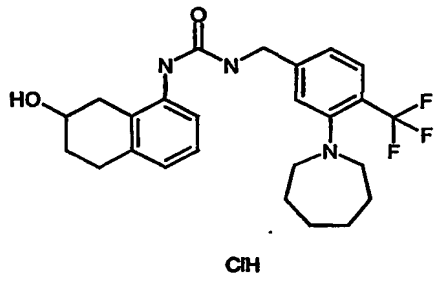
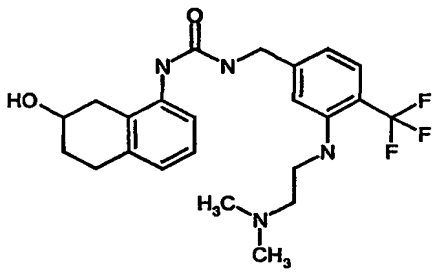
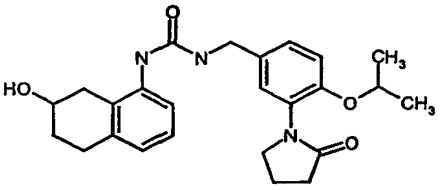
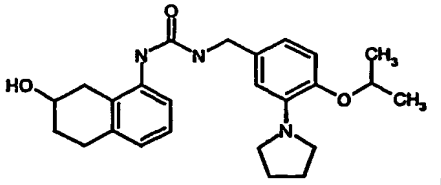
mp 162.9 °C;
Molecular weight : 447.50
MS (M+H): 448
Activity grade:A

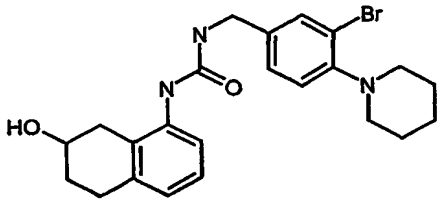
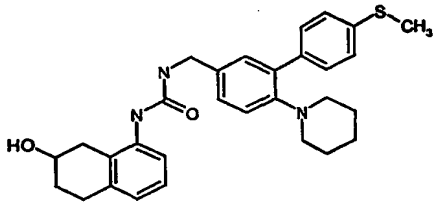
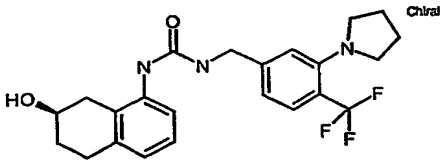
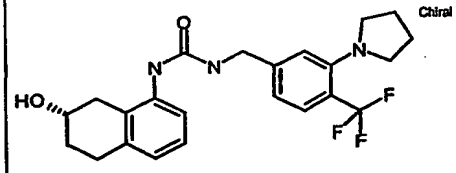
In the similar manner as described in Example 1-1, compounds in Example 1-2 to 1-23 as shown in Table 1 were synthesized.

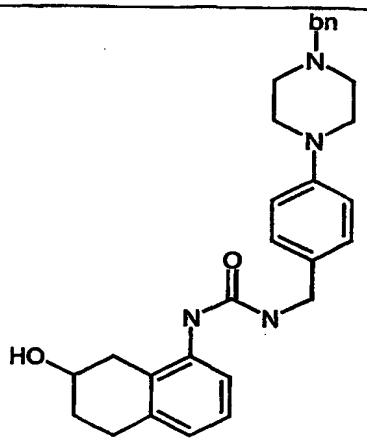
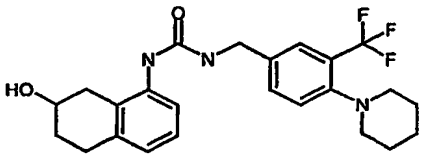
BAY NO	MOLSTRUCTURE	MW	MS (M+H)	MP	IC50
1-2		365,4794	366	>145Z	A
1-3		367,4517	368	>200Z	C
1-4		401,8967	402	>113Z	A
1-5		379,5065	380	147,9	A

BAY NO	MOLSTRUCTURE	MW	MS (M+H)	MP	IC50
1-6		381,4788	382	239.3-243.2	B
1-7		365,4794	366	194.7-196.7	A
1-8		469,9387	470	100	
1-9		433,4778	434	180,5	

BAY NO	MOLSTRUCTURE	MW	MS (M+H)	MP	IC50
1-10		433,4778	434	170,2	A
1-11		469,9387	470	65,2	A
1-12		461,532	462	144,8	A
1-13		461,532	462	92	A

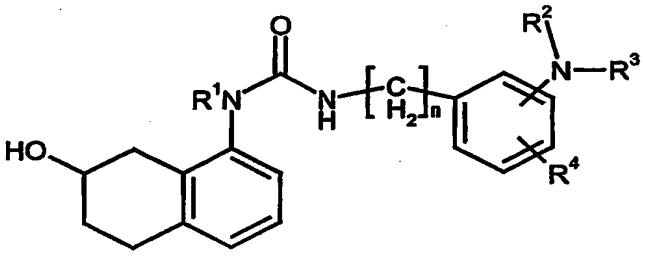
BAY NO	MOLSTRUCTURE	MW	MS (M+H)	MP	IC50
1-14		497,9929	498	83	A
1-15		450,5084	451	90	A
1-16		437,5435	438	70	C
1-17		423,5601	424	119	A

BAY NO	MOLSTRUCTURE	MW	MS (M+H)	MP	IC50
1-18		458,4025	459	150-152	A
1-19		501,6964	502	113-115	A
1-20		433,4778	434	196,6	A
1-21		433,4778	434	160,6	A

BAY NO	MOLSTRUCTURE	MW	MS (M+H)	MP	IC50
1-22		470,6199	471	112-114	B
1-23		447,5049	448	153,4	

Claims

1. A tetrahydro-naphthalenyl derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



(I)

wherein

n represents an integer of 0 to 6;

R^1 represents hydrogen or C_{1-6} alkyl;

R^2 and R^3 are identical or different and represent hydrogen, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkyl-amino, di(C_{1-6} alkyl)amino, or mono-, di-, or tri- halogen,

or

R^2 and R^3 together with the nitrogen atom to which they are attached, form a 3-8 membered saturated heterocyclic ring optionally interrupted by one or two atoms selected from the group consisting of oxygen, sulfur and nitrogen;
wherein
said saturated heterocyclic ring is optionally having substituents selected from the group consisting of halogen, hydroxy, amino, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, and benzyl; and

R^4 represents hydrogen halogen, C_{1-6} alkyl optionally substituted by mono-, di-, or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen or C_{1-6} alkylthio.

2. The tetrahydro-naphthalenyl derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

n represents an integer of 0 or 1;

R^1 represents hydrogen;

R^2 and R^3 are identical or different and represent hydrogen, or C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, or mono-, di-, or tri- halogen,

or

R^2 and R^3 together with the nitrogen atom to which they are attached, form a 5-7 membered saturated heterocyclic ring optionally interrupted by one or two atoms selected from the group consisting of oxygen, and nitrogen,
wherein
said saturated heterocyclic ring is optionally having substituents selected from the group consisting of oxo, C_{1-6} alkyl, and benzyl; and

R^4 represents hydrogen halogen, C_{1-6} alkyl optionally substituted by mono-, di-, or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen or C_{1-6} alkylthio.

3. The tetrahydro-naphthalenyl derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

n represents an integer of 0 or 1;

R^1 represents hydrogen;

R^2 represents hydrogen or C_{1-6} alkyl;

R^3 represents hydrogen, or C_{1-6} alkyl optionally substituted by amino, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino,

or

R^2 and R^3 together with the nitrogen atom to which they are attached, form a pyrrolidinyl optionally substituted by oxo, piperidino, piperazinyl optionally substituted by benzyl, homopiperidino, or morpholinyl; and

R^4 represents hydrogen, fluoro, chloro, bromo, C_{1-6} alkyl optionally substituted by mono-, di-, or tri- halogen, C_{1-6} alkoxy or C_{1-6} alkylthio.

4. The tetrahydro-naphthalenyl derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein said tetrahydro-naphthalenyl derivative of the formula (I) is selected from the group consisting of:

N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[3-(1-piperidinyl)-4-(trifluoromethyl)benzyl]urea;

N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[3-(1-pyrrolidinyl)-4-(trifluoromethyl)benzyl]urea;
N-[4-(1-azepanyl)-3-(trifluoromethyl)benzyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-[3-(1-azepanyl)-4-(trifluoromethyl)benzyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-[3-bromo-4-(1-piperidinyl)benzyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-{[4'-(methylsulfanyl)-6-(1-piperidinyl)-1,1'-biphenyl-3-yl]methyl}urea; and
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[3-(1-pyrrolidinyl)-4-(trifluoromethyl)benzyl]urea.

5. A tetrahydro-naphthalenyl derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in any one of claims 1 to 4 for the treatment and/or prophylaxis of diseases.

6. A medicament comprising at least one of the compounds, their tautomeric and stereoisomeric form, and salts thereof as claimed in claim 1 to 4 in combination with at least one pharmaceutically acceptable carrier and/or excipients.

7. The medicament as claimed in claim 6, wherein said tetrahydro-naphthalenyl derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof is a VR1 antagonist.

8. The medicament as claimed in claim 6 for the treatment and/or prophylaxis of a disease selected from the group consisting of urinary incontinence, urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia,

nerve injury, ischaemia, neurodegeneration, stroke, inflammatory disorders, asthma and COPD.

9. Use of compounds of any one of claims 1 to 4 for the production of a medicine for treatment and/or prophylaxis of a disease selected from the group consisting of urinary incontinence, urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, inflammatory disorders, asthma and COPD.

10. An agent to treat and/or prevent urological disorder or diseases; comprising the compound, its tautomeric and stereoisomeric form, or physiologically acceptable salts thereof as claimed in claim 1 as an active ingredient.

11. An agent to treat and/or prevent pain; comprising the compound, its tautomeric and stereoisomeric form, or physiologically acceptable salts thereof as claimed in claim 1 as an active ingredient.

12. An agent to treat and/or prevent inflammation; comprising the compound, its tautomeric and stereoisomeric form, or physiologically acceptable salts thereof as claimed in claim 1 as an active ingredient.

TETRAHYDRO-NAPHTHALENE DERIVATIVES

ABSTRACT

This invention relates to tetrahydro-naphthalene derivatives and salts thereof which is useful as an active ingredient of pharmaceutical preparations.

The tetrahydro-naphthalene derivatives of the present invention have an excellent activity as VR1 antagonist and useful for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urinary incontinence, urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, inflammatory disorders, asthma and COPD.